Hemophagocytic Lymphohistiocytosis: A Rare Cause of Pancytopenia

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Abstract

A 36-year-old man with fever and pancytopenia due to Hemophagocytic Lymphohistiocytosis is reported. The patient was started on the HLH-94 based treatment. Two weeks after the initiation of therapy the patient's pancytopenia had resolved and he was discharged to complete treatment as an outpatient. The initial clinical presentation, diagnostic criteria, pathophysiology and treatment will be discussed.

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare syndrome seen almost exclusively in children under five years of age.[1,2] The syndrome develops as a result of an uncontrolled histiocyte activation and proliferation into multiple organ systems. The syndrome is defined by the presence of fever, cytopenia (2 of 3 cell lines), splenomegaly, hypofibrinogenemia and/or hypertriglyceridemia and hemophagocytosis seen on microscopic examination.[3] It develops either from a primary, inherited condition know as Familial Hemophagocytic Lymphohistiocytosis (FHL) or a secondarily acquired form. The latter are infection-associated hemophagocytic syndrome (IAHS) caused by any variety of bacterial, viral, fungal or parasitic organisms, or malignancy-associated hemophagocytic syndrome (MAHS) typically associated with acute lymphocytic leukemia or lymphoma. Although the initial treatment is the same, the prognosis and definitive treatments vary based on the underlying etiology.

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Case Report

A 36-year-old active duty Navy Filipino man stationed in Japan complained of a three-day history of persistent headache and fever to 104°F despite repeated doses of acetaminophen. He had no ill contacts and no rodents or mosquitoes exposures. Initial work up at his local medical clinic was unrevealing and the sailor was sent home. He returned the following day with persistence of his fever, was found to be leukopenic and was transferred to our medical center. His review of systems was otherwise unremarkable and physical exam was significant for splenomegaly without peripheral adenopathy. No rash was noted and the remainder of his physical exam was normal. Initial laboratory studies were significant for an elevated ferritin of 5873 ng/ml, fibrinogen 197 mg/dl, WBC 1700, hemoglobin 10.4 g/dl, hematocrit 30.2%, platelet count 16,000, LDH 998 U/L (normal range: 94-250). Additional abnormal laboratory results include an AST of 165 U/L (normal: 0-37), ALT: 87 (normal: 0-40), alkaline phosphatase of 538 U/L (normal: 38-126) and a conjugated bilirubin of 5.3 mg/dl.

Peripheral blood smear obtained on admission was significant for leukopenia, neutropenia and thrombocytopenia. Bone marrow aspirate was remarkable for normal cellularity without blasts. However, multiple histiocytes were seen with ingested leukeocytes, erythrocytes and platelets. The diagnosis of Hemophagocytic lymphohistiocytosis (HLH) was made based on clinical presentation, the presence of all diagnostic criteria (table 1)[3] and the observation of phagocytic histiocyte cells on bone marrow biopsy (figure 1). The patient was started on dexamethasone and etoposide per the Hemophagocytic Lymphohistiocytosis Study Group-94 guidelines, as well as high-dose intravenous acyclovir. There was an immediate resolution of the patient's fever, and hemoglobin, platelet and leukocyte counts demonstrated a brisk response to the initial therapy. Peripheral blood PCR for Epstein Barr virus (EBV) DNA was positive. He did not test positive for any of the familial gene mutations. He was discharged for completion of his chemotherapy and antiviral course as an outpatient.

Discussion

Pathophysiology

Although the exact event that triggers activation of the Natural Killer (NK) and Cytotoxic T cells is not clearly understood, it is theorized that an uncontrolled expansion of polyclonal CD8 T lymphocytes and subsequent cytokine storm cause the non-specific T cell activation of macrophages/ histiocytes.[4] This reaction results in the observed non-malignant invasion of visceral organs, lymph nodes and bone marrow. The non-specific activation also leads to phagocytosis of all hematopoietic precursors by invading histiocytes.

Excess production of TNF-a and a soluble Fas ligand (CD95: a mediator for cellular apoptosis) cause the tissue damage and inflammation seen specifically in the liver and spleen.

In Familial HLH, there is an inherited loss of function in NK/cytotoxic T cells. The most frequent gene mutations seen in FHLH are in the Perforin Gene (PRF-1 [10q 21-22], a gene for direct cellular killing) and a mutation in Ch 9q21.3-22. T cell dysfunction is a constant feature of primary HLH and does not change after treatment with HLH-94 protocol. This is an important distinction as it has consequences on treatment success.[1]

In EBV associated HLH it is believed that infection of T cells results in the overproduction of cytokines IL-1, 2, 6, 10, interferon gamma and TNF-α, which cause excessive activation of macrophage cell lines.[5] In all etiologies, researchers find macrophages with increased expression of CD-36, a key phagocytosis receptor with a lack of antigen presenting ability.[6]

Diagnostic Criteria

Hemophagocytic Lymphohistiocytosis (HLH) is a syndrome defined by the presence of five findings:

Table 1.— Diagnostic Criteria for Hemophagocytic Lymphohistiocytosis

1. Persistent fever: seen in 60-100% of cases
2. Cytopenia affecting two of the three cell lines: seen in 82-100% of cases
3. Splenomegaly: seen in 35-100% of cases
4. Hypofibrinogenemia: seen in 19-85% of cases and/or hypertri glyceridemia: seen in 59-100% of cases
5. Hemophagocytosis as seen on bone biopsy : 100% (required for diagnosis)

Hepatic dysfunction is present in 74 percent of cases. Additional findings that have been proposed to assist in diagnosis are: low/absent NK-cell activity; serum ferritin >500 μg/L, and soluble CD25 (sIL-2 receptor) >2400 U/ml. In patients with neurologic involvement, a predominance of mononuclear cells in the CSF with chronic inflammatory changes on liver biopsy and reduced natural killer activity is also highly suggestive of the syndrome.

Patients may not meet all diagnostic criteria on initial presentation, so retesting is essential. This is particularly important in the evaluation for hemophagocytic histiocytes. Initial bone marrow biopsies may be inconclusive so it is recommended that repeated samples be taken. Alternatively, spleen, lymph nodes and or liver biopsies are recommended if clinical suspicion is high and initial bone marrow biopsy is negative.[3]

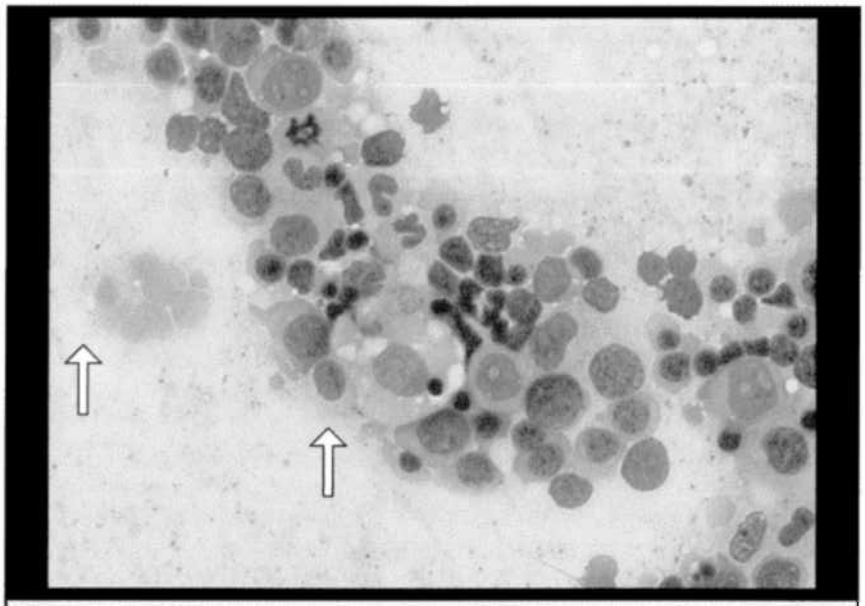

Figure 1.— Bone marrow aspirate from the patient. Arrows indicate two Hemophagocytic histiocytes with ingested hematopoietic cells, erythrocytes, leukocytes, and platelets

Treatment

Initial management: During the evaluation for HLH syndrome and continuing into the initial treatment it is essential to provide basic supportive care. This includes replacement of red blood cells, platelets, and fibrinogen. These corrections are often short-lived secondary to hypersplenism and fever. Maintenance of neutropenic precautions and aggressive treatment of all infections is also important. Currently, initial treatment with chemotherapy is the standard. This treatment focuses on the immune suppression and disruption of the aberrant signaling pathways. HLH-94 treatment protocol consists of an initial eight weeks of biweekly etoposide doses and a dexamethasone taper. During weeks 10 through 52 the patient receives etoposide and dexamethasone pulse every other week and twice daily Cyclosporine A with a target serum concentration of 200 mcg/L.

In secondary HLH syndrome the causative etiology needs to be identified and addressed. Primary HLH syndrome will require bone marrow transplant for definitive treatment, since relapse after treatment occurs in all cases.[1] Identification of the underlying cause of this syndrome is essential as primary and secondary disease have different end points. Furthermore, among the infectious etiology, the EBV etiologies differ in that these patients have a worse prognosis as compared to all other infections.[6]

Summary

Hemophagocytic Lymphohistiocytosis is a rare disease seen primarily in children with one study estimating the incidence to be 1.2 cases in 1 million.[3] Although this syndrome is an uncommon cause of pancytopenia, the diagnosis of HLH should be considered especially in the setting of hepatic dysfunction and splenic enlargement. The prognosis is poor if the syndrome is not promptly treated (median survival without treatment of two months).[7] In addition, most forms of secondary HLH syndrome are very amenable to treatment.[3,7] It is also important to remember that although the syndrome is defined by the presence of five criteria, all markers may not be present on presentation. In the absence of any one specific clinical marker and a high clinical suspicion, therapy should commence immediately and testing should continue.[3,4] Diagnostic work up and treatment of possible underlying malignancy such as acute lymphocytic leukemia, myeloma, lymphoma,

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and carcinoma or determining the causative infectious agent is critical as well. It is also important to remember that the presence of EBV virus or other infectious agents does not preclude underlying FHLH and genetic testing is recommended for all cases.[8] Ultimately in FHLH, after initial treatment with the chemotherapy, the ultimate curative therapy is allogeneic bone marrow transplant. Our patient has done very well and is completing his therapy, without return of the syndrome.

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